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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) Title: SYNTHESIS OF CC-1065/DUOCARMYCIN ANALOGS

(57) Abstract

The dihydroindole C–ring found in CC–1065/duocarmycin analogs is formed by the 5–*exo–trig* radical cyclization of an aryl halide onto a tethered vinyl chloride forming with chlorine installed as a suitable leaving group for subsequent cyclopropane spirocyclization. The versatility of this approach is disclosed in the context of six CC–1065/duocarmycin analogs previously synthesized in this laboratory.

SYNTHESIS OF CC-1065/DUOCARMYCIN ANALOGS

Description

Technical Field:

The present invention relates to a method for the
synthesis of the dihydroindole C-ring found in CC-1065 /
duocarmycin analogs. More particularly, the invention

5   comprises the 5-exo-trig radical cyclization of an aryl halide
onto a tethered vinyl chloride forming the dihydroindole C-
ring with chlorine installed as a suitable leaving group for
subsequent cyclopropane spirocyclization. The versatility of
this approach is examined in the context of six CC-1065 /

10   duocarmycin analogs previously synthesized in this laboratory.

Background:

CC-1065 (1; Chidester et al. J. Am. Chem. Soc. 1981, 1-3,
7629) and the duocarmycins 2 (Ichimura et al. J. Antibiot.

15   1990, 43, 1037) and 3 (Takahashi et al. J. Antibiot. 1988, 41,
1915; Yasuzawa et al. Chem. Pharm. Bull. 1995, 43, 378) are
the parent members of a potent class of antitumor antibiotics
that derive their biological properties through reversible,
sequence selective alkylation of DNA (For a review of

20   mechanistic aspects see: Boger, et al. Angew. Chem., Int. Ed.
Engl. 1996, 35, 230).

Since their disclosure, synthetic efforts have focused on
the natural products as well as a great number of rationally
designed analogs (For a review of synthetic efforts see: Boger

25   et al. Chem. Rev., 1997, 97, 787). These analogs have served
define the fundamental principles underlying the relationships
between structure, chemical reactivity and biological
properties within this family, and have advanced the
understanding of the origin of sequence selectivity and the

30   catalysis of the DNA alkylation reaction by 1-3 (Boger et al.
J. Am. Chem. Soc. 1997, 119, 4977; Boger et al. J. Am. Chem.

Soc. *1997*, *119*, 4987; Boger et al. *Biorg. Med. Chem.* *1997*, *5*,
263; Warpehoski et al. *J. Am. Chem. Soc.* *1994*, *116*, 7573;
Warpehoski et al. *J. Am. Chem. Soc.* *1995*, *117*, 2951).

5   Common synthetic routes to many of the duocarmycin and
CC-1065 analogs incorporate the same transformation via a four
step procedure highlighted by an *in-situ* trap of a primary
radical with TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-
piperidinyloxy free radical) followed by its reductive removal
10 and conversion to the chloride as depicted for the synthesis
of CBI (Boger et al. *J. Org. Chem.* *1995*, *60*, 1271) as
illustrated in Figure 4.

It would be beneficial to have a more direct and higher
yielding transformation to obtain the dihydroindole C-ring
15 found in CC-1065 / duocarmycin analogs. What is needed,
therefore, is an efficient and general method for the
synthesis of the dihydroindole C-ring found in CC-1065 /
duocarmycin analogs with less steps than the standard four
step TEMPO procedure as described above.

20

Summary of the Invention:

One aspect of the invention is directed to a 2 step
synthesis of the dihydroindole C-ring found in CC-1065 /
duocarmycin analog. An aryl halide is alkylated with 1,3-
25 dichloropropene and a catalytic amount of n-tetrabutylammonium
iodide for forming a vinyl chloride. The vinyl chloride is
then cyclized under conditions using tribuytyl tin hydride,
catalytic AIBN and toluene as the solvent for forming the
dihydroindole C-ring of the CC-1065/duocarmycin analog.

30

Another aspect of the invention is directed to the
following compounds:

HN—⟋ ⟍CH₂Cl

BnO— N BOC

and

MeO OMOM ⟍CH₂Cl

Me— OMe N BOC
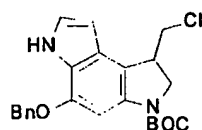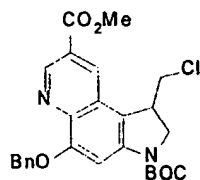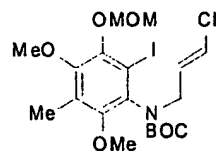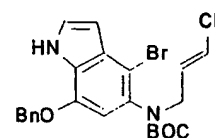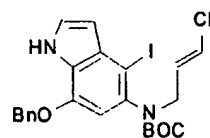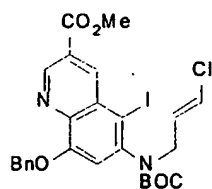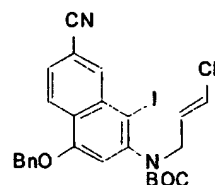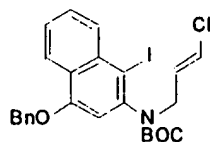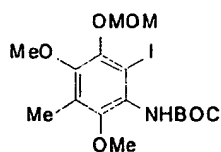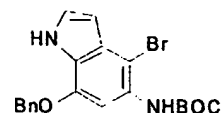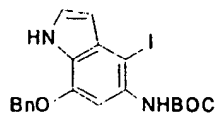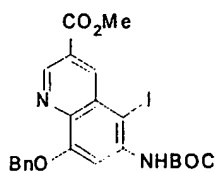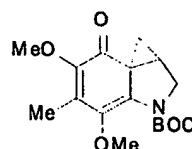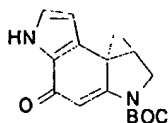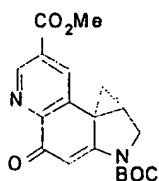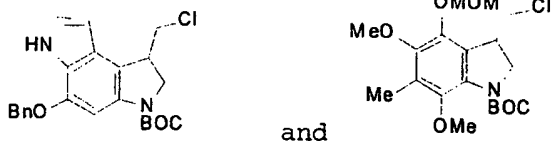
Description of Figures:

Figure 1 shows CC-1065 (1) and the duocarmycins (2) and (3). The compounds are parent members of a potent class of antitumor antibiotics.

5   Figure 2 shows CBI (4) (5), CPyI (6), desmethyl-CPI (7), iso-CBI (8), and the mitomycin-hybrid (9) which are compounds of interest in this application.

Figure 3 shows the novel intramolecular aryl radical cyclization onto a tethered vinyl chloride to install the

10 dihydroindole C ring with chlorine installed as a suitable leaving group for subsequent cyclopropane spirocyclization.

Figure 4 shows the standard four step procedure highlighted by an in-situ trap of a primary radical with TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical)

15 followed by its reductive removal and conversion to the chloride as depicted for the synthesis of CBI.

Figure 5 illustrates the transformation from compound 10a to 12a and the subsequent formation of a cyclopropyl ring.

Figure 6 shows a table which illustrates the results of

20 the two-step synthesis of 3-chloro-methylindolines with the following conditions: a NaH, 1,3-dichloropropene, DMF, 25 °C; b NaH, 1,3-dichloropropene, nBu₄NI, DMF, 25 °C; c AIBN (cat.), Bu₃SnH, benzene, 60-75 °C; d AIBN (cat.), Bu₃SnH, toluene, 90°C wherein each compound uses the same transformation as

25 shown in Figure 6.

Detailed Description of the Invention

The invention is directed to a two-step transformation
directed to the synthesis of 6 CC-1065/duocarmycin analogs
using a novel intramolecular aryl radical cyclization onto a
5   vinyl chloride to form the dihydroindole C-ring found in 6
CC-1065/duocarmycin analogs. This transformation represents a
potential two-step improvement to the synthetic route to many
other analogs, which most recently incorporated the same
transformation via a four step procedure highlighted by an *in-
10   situ* trap of a primary radical with TEMPO (TEMPO = 2,2,6,6-
tetramethyl-1-piperidinyloxy free radical) followed by its
reductive removal and conversion to the chloride as depicted
for the synthesis of CBI (Boger et al. *J. Org. Chem.* 1995, *60*,
1271) as illustrated in Figure 4.

15   Patel et al. describes the synthesis of an analog named
Oxa-duocarmycin SA which utilizes a novel intramolecular aryl
radical cyclization onto a tethered vinyl chloride to install
the dihydroindole C ring with chlorine installed as a suitable
leaving group for subsequent cyclopropane spirocyclization as
20   described in Figure 3.

Application of this improved two-step transformation to the
synthetic routes reported for a number of the analogs synthesized
in this laboratory would serve to establish the versatility of
this approach to the synthesis of CC-1065 and duocarmycin
25   analogs.

With this goal in mind, the C-ring construction for CBI (4;
Boger et al. *J. Org. Chem.* 1995, *60*, 1271, CCBI (5; Boger et al.
J. Org. Chem. 1996, *61*, 4894), CPyI (6), desmethyl-CPI (7), *iso-*
CBI (8), and the mitomycin-hybrid (9) was investigated. The
30   appropriately functionalized aryl halides (10a-g), which were
obtained either through direct electrophilic halogenation
(entries 1-5) or directed ortho metallation (entries 6 and 7) and
halide quench, were alkylated with 1,3 dichloropropene to

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complete the radical cyclization precursors (11a-g) in high yields. Treatment with Bu₃SnH and a catalytic amount of AIBN (AIBN = 2,2'-azobisisobutyronitrile) with heating in benzene or toluene very cleanly effected 5-*exo-trig* radical cyclization to
5   form the 3-chloromethyl indoline C-ring present in each of the analogs (12a-g) as illustrated in Figure 6.

This two-step transformation works well with benzene, naphthalene, indole and quinoline derivatives, aryl iodides as well as aryl bromides, with little to no deterioration in the
10 consistently high yields for both steps. Brief optimization efforts revealed that higher yields may sometimes be obtained with addition of n-Bu₄NI to the alkylation reaction, as well as substitution of toluene and higher reaction temperature for benzene. It was observed, as also noted by Patel et al. that
15 deoxygenation of the solvent prior to radical cyclization may enhance both the rate and yield of the reaction.

In summary, this novel intramolecular aryl radical cyclization onto a vinyl chloride, as introduced by Patel, was successfully applied to the C-ring synthesis of 6 CC-
20 1065/duocarmycin analogs. This application has effectively shortened the synthesis of each of these analogs by two steps. Clearly the versatility of this approach, combined with the high conversions for both steps, assure its use in future rational analog design in the CC-1065/duocarmycin family of antitumor
25 antibiotics.

While a preferred form of the invention has been shown in the drawings and described, since variations in the preferred form will be apparent to those skilled in the art, the invention should not be construed as limited to the specific form shown and
30 described, but instead is as set forth in the following claims.

EXPERIMENTAL PROTOCALS

General ¹H and ¹³C nmr spectra were recorded either on a Bruker AM-250, a Bruker AMX-400 or a Bruker AMX-500

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spectrometer. Residual protic solvent CHCl$_3$ (δ_H = 7.26 ppm, δ_c = 77.0), d$_4$-methanol (δ_H = 3.30 ppm, δ_c = 49.0) and D$_2$O (δ_H = 4.80 ppm, δ_c (of CH$_3$CN) = 1.7 ppm) or TMS (δ_H = 0.00 ppm) were used as internal reference. Coupling constants were measured in Hertz

5   (Hz). HRMS were recorded using FAB method in a m-nitrobenzylalcohol (NBA) matrix doped with NaI or CsI. Infra-red spectra were recorded on a Perkin-Elmer FTIR 1620 spectrometer. Enantiomeric excess was determined by HPLC using a Daicel Chemical Industries CHIRALPAK AD column. Optical

10 rotations were measured with an Optical Activity AA-1000 polarimeter. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh). Analytical thin layer chromatography was performed

15 using pre-coated glass-backed plates (Merck Kieselgel F$_{254}$) and visualized by cerium molybdophosphate or ninhydrin. Diethyl ether, tetrahydrofuran (THF) and toluene (PhCH$_3$) were distilled from sodium-benzophenone ketyl, dichloromethane (DCM) and acetonitrile from calcium hydride. Other solvents and reagents

20 were purified by standard procedures if necessary.

General Experimental Procedure for individual synthesis of 12a-g as shown in Figure 6: A solution of the aryl iodide (one of **10a-g** as shown in Figure 6 obtained from the sources or conditions as described herein; aryl iodide is obtained

25 from the following sources:) in anhydrous DMF (0.1M) at 0 °C was treated with NaH (2.0 equiv.) in small portions. The resulting suspension was stirred 15 min and treated with neat 1,3-dichloropropene (5.0 equiv) in a slow dropwise manner, followed by catalytic Bu$_4$NI (0.1 equiv.; n-tetrabutylammonium

30 iodide). The reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was quenched with the addition of 5% aqueous NaHCO$_3$, and the aqueous layer was extracted with EtOAc. The combined organic extracts were

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washed with H$_2$O, dried (Na$_2$SO4) and concentrated under reduced
pressure. The crude was purified by flash column
chromatography. A solution of one of **11a-g** in anhydrous
benzene (0.1M; alternatively substitution of toluene and
5   higher reaction temperature can optimize yield, due to higher
temperatures) was treated with Bu$_3$SnH (1.05 equiv.) and
catalytic AIBN (0.1 equiv.) and deoxygenated with a stream of
dry N$_2$ gas. The solution was heated to 80 °C for 2 h and
concentrated *in vacuo*. The crude was purified by flash column
10   chromatography to form one of compounds **12a-g**.

Synthesis of cyclopropane via spirocyclization. The chlorine
group of the dihydroindole C-ring is installed as a suitable
leaving group for cyclopropane spirocyclization.
15   Methodologies for subsequent spirocyclization and further
aklyation of the resultant cyclopropane C-ring system to the
DNA portion of CC-1065 and the duocarmycins is well known in
the art. A representative spirocyclization is accomplished
via treatment of **12(a-g)** with NaH (3 equiv, THF, 0 °C, 30 min)
20   to provide (**4-9**; as shown in Figure 2). Similarly,
acid-catalyzed deprotection of **12(a-g)** (3N HCl-EtOAc, 25 °C,
20 min) followed by spirocyclization of the crude indoline
hydrochloride salt upon exposure to 5% aqueous NaHCO$_3$-THF (1:1,
25 °C, 1.5 h, 93%) can also provide (**4-9**; as shown in Figure
25   **2**).

Synthesis of compounds 4-9 as shown in Figure 2
A solution of **12(a-g**; one of the compounds in Figure 6;
obtained from the sources or conditions as described herein)
30   (1.5 mg, 4.1 μmol) in tetrahydrofuran-dimethylformamide (3:1,
200 μL) at 0 °C under N$_2$ was treated with suspension of NaH
(0.5 mg, 60% in an oil dispersion, 12 μmol, 3 equiv). The
reaction mixture was allowed to stir at 0 °C and for 30 min

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before the addition of pH 7 phosphate buffer (0.2 M, 250 μL) and 2 mL of tetrahydrofuran. The organic layer was dried (Na₂SO₄) and concentrated in vacuo. Chromatography (SiO₂, 20-30% Ethylacetate-hexane gradient elution) afforded (4-9; as shown in Figure 2): Alternative Spyrocyclization: 12(a-g; one of the compounds)(5 mg, 1.37 μmol) was treated with anhydrous 3N HCl-Ethylacetate (0.4 mL) at 24 °C for 20 min. The solvent was removed in vacuo to afford the crude, unstable amine hydrochloride. This residue was treated with 5% aqueous NaHCO₃ (0.4 mL) and tetrahydrofuran (0.4 mL) at 24 °C under N₂, and the two phase mixture was stirred for 1.5 h (24 °C). The reaction mixture was extracted with Ethylacetate (3 x 2 mL) and the combined extracts were washed with H₂O (2 mL), dried (Na₂SO₄) and concentrated in vacuo. Chromatography (SiO₂, 10% CH₃OH-CH₂Cl₂) afforded (4-9; as shown in Figure 2).

-10-
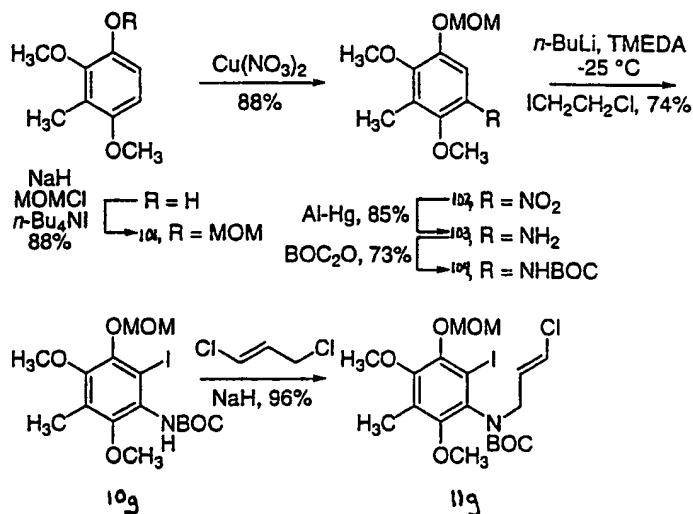
2,4-(Dimethoxy)-3-(methyl)-methoxymethyl phenyl ether (101).

A solution of 2,4-(dimethoxy)-3-methylphenol (1.0 g, 5.95 mmol) in 60 mL of anhydrous DMF at 0 °C was treated with NaH (357 mg, 9.91 mmol) in several portions over 5 min. After 10 min, Bu$_4$NI (219 mg, 0.60 mmol) was added followed by the dropwise addition of ClCH$_2$OCH$_3$ (0.68 mL, 8.91 mmol). The reaction mixture was stirred at 25°C for 36 h before the reaction was quenched by the slow addition of 30 mL of H$_2$O. The aqueous layer was extracted with EtOAc (3 (30 mL). The organic layers were combined, washed with 10% aqueous NaHCO$_3$ (50 mL) and H$_2$O (4 (20 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. Flash chromatography (SiO$_2$, 3 (10 cm, 10% EtOAc/hexane) provided **101** (1.11 g, 88%) as a light yellow oil: ^{1}H NMR (CDCl$_3$, 250 MHz) δ 6.92 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 5.13 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.50 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ 153.5, 149.2, 144.3, 121.0, 114.4, 105.3, 96.0, 60.4, 56.0, 55.7, 8.9; IR (film) ν$_{max}$ 2937, 2833, 1595, 1487, 1440, 1420 cm^{-1}; FABHRMS (NBA) m/z 212.1040 (C$_{11}$H$_{16}$O$_4$ requires 212.1049).

2,4-(Dimethoxy)-3-(methyl)-5-(nitro)-methoxymethyl phenyl ether (102).

A solution of **101** (1.11 g, 5.21 mmol) in 18 mL freshly distilled Ac$_2$O at 0°C was treated with Cu(NO$_3$)$_2$•2.5 H$_2$O (2.41 g, 10.4 mmol) in several portions over 5 min. The reaction mixture was stirred for 2 h at 0 °C, then 1 h at 25 °C before the reaction was poured over H$_2$O (50 mL) and extracted with EtOAc (3 (30 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude light yellow oil (1.18 g, 88%) was carried on to the next transformation: ^{1}H NMR (CDCl$_3$, 250 MHz) δ 7.54 (s, 1H), 5.18 (s, 2H), 3.87 (s,

3H), 3.81 (s, 3H), 3.48 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (CDCl$_3$,
62.5 MHz) δ 153.0, 147.8, 145.8, 138.9, 128.2, 110.5, 95.3,
61.8, 60.5, 56.2, 9.5; IR (film) ν$_{max}$ 2942, 2829, 1522, 1481,
1344, 1280, 1246 cm^{-1}; FABHRMS (NBA) m/z 258.0977 (C$_{11}$H$_{15}$NO$_6$ +
H$^+$ requires 258.0978).

5-(Amino)-2,4-(dimethoxy)-3-(methyl)-methoxymethyl phenyl
ether (103).

A solution of 102 (1.18 g, 4.57 mmol) in 90 mL moist
ether (8:2:1 Et$_2$O:EtOH:H$_2$O) was cooled to 0°C, and treated with
freshly prepared Al-Hg (1.23 g Al, 45.7 mmol) in small 1 (1
cm pieces. The reaction mixture was stirred vigorously for
0.5 h at 0 (C, then 1 h at 25 (C. The reaction mixture was
then filtered through Celite, and the Celite was washed
thoroughly with Et$_2$O (5 (20 mL). The solution was then washed
with saturated aqueous NaCl (100 mL), dried (Na$_2$SO$_4$), and
concentrated under reduced pressure to afford 103 (0.88 g,
85%) as a crude brown oil, which was immediately carried on to
the next step: ^{1}H NMR (CDCl$_3$, 250 MHz) δ 6.42 (s, 1H), 5.11 (s,
2H), 3.70 (s, 3H), 3.66 (s, 3H), 3.56 (m, 2H), 3.47 (s, 3H),
2.16 (s, 3H); ^{13}C NMR (CDCl$_3$, 250 MHz) δ 147.0, 140.4, 140.3,
135.8, 125.4, 102.0, 95.4, 60.6, 59.4, 56.0, 9.34; IR (film)
ν$_{max}$ 3446, 3359, 2935, 2826, 1617, 1492, 1358 cm^{-1}; ESIMS m/z
228 (C$_{11}$H$_{17}$NO$_4$ + H$^+$ requires 228).

[N-(tert-Butyloxycarbonyl)amino]-2,4-(dimethoxy)-5-
(methoxymethoxy)-3-methylbenzene (104).

A solution of crude 102 (0.88 g, 3.85 mmol) in 40 mL
anhydrous THF was treated with BOC$_2$O (1.73 g, 7.72 mmol) and
the reaction mixture was warmed at reflux (65 (C) for 18 h.
The solvents were removed under reduced pressure, and flash
chromatography (SiO$_2$, 3 (10 cm, 10% EtOAc/hexane) provided

pure **104** as a yellow oil (0.96g, 76%): ^{1}H NMR (CDCl$_3$, 250 MHz)
δ 7.72 (br s, 1H), 6.86 (br s, 1H), 5.18 (s, 2H), 3.75 (s,
3H), 3.67 (s, 3H), 3.51 (s, 3H), 2.19 (s, 3H), 1.50 (s, 9H);
^{13}C NMR (CDCl$_3$, 100 MHz) δ 152.7, 146.4, 143.6, 141.6, 127.8,
124.8, 105.3, 95.5, 80.4, 60.5, 60.4, 56.4, 28.3, 9.5; IR
(film) ν$_{max}$ 3437, 3341, 2977, 2935, 1731, 1519, 1454, 1422,
1397 cm^{-1}; FABHRMS (NBA/CsI) *m/z* 460.0723 (C$_{16}$H$_{25}$NO$_6$ + Cs$^+$
requires 460.0736).

**[*N*-(tert-Butyloxycarbonyl)amino]-2,4-(dimethoxy)-6-(iodo)-5-(m
ethoxymethoxy)-3-methyl benzene (10g).** A solution of **104**
(0.55 g, 1.67 mmol) in 6.6 mL anhydrous THF was cooled to -25
(C and treated with TMEDA (0.94 mL, 6.18 mmol) followed by
n-BuLi (2.5 mL of a 2.5 M solution in hexane, 6.18 mmol) in a
slow dropwise manner. The resulting gold solution stirred for
2 h at -25 (C. The reaction mixture was treated with
1-chloro-2-iodoethane (0.45 mL, 6.18 mmol) and stirred for 15
min at 25 (C. The reaction was diluted with H$_2$O (50 mL) and
extracted with Et$_2$O (3 (30 mL), and the combined organic
extracts were washed with saturated aqueous NaCl, dried
(Na$_2$SO$_4$), and concentrated under reduced pressure. Flash
chromatography (SiO$_2$, 2.5 (10 cm, 20% EtOAc/hexane) yielded
11g (560 mg, 74%) as a colorless oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ
5.99 (br s, 1H), 5.10 (s, 2H), 3.75 (s, 3H), 3.69 (s, 3H),
3.65 (s, 3H), 2.17 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (CDCl$_3$, 100
MHz) δ 153.6, 151.8, 150.5, 146.9, 129.3, 126.7, 99.1, 95.8,
80.6, 60.5, 60.3, 58.5, 28.3, 9.8; IR (film) ν$_{max}$ 3321, 2975,
2936, 1722, 1485, 1455, 1390 cm^{-1}; FABHRMS (NBA/CsI) *m/z*
585.9688 (C$_{16}$H$_{24}$INO$_6$ + Cs$^+$ requires 585.9703).

**[*N*-(tert-Butyloxycarbonyl)-*N*-(3-chloro-2-propen-1-yl)amino]-2,
4-(dimethoxy)-6-(iodo)-5-(methoxymethoxy)-3-methylbenzene**

(11g).

A solution of **10g** (0.610 g, 1.34 mmol) in 13.4 mL
anhydrous DMF was cooled to 0 (C, and treated with NaH (60%
dispersion in oil, 121 mg, 4.03 mmol) in small portions. The
resulting suspension was stirred for 15 min and treated with
neat 1,3-dichloropropene (0.52 mL, 5.5 mmol) in a slow
dropwise manner, followed by catalytic n-Bu$_4$NI (50.0 mg, 0.13
mmol). The reaction mixture was warmed to 25 (C and stirred
for 3 h. The reaction mixture was quenched with the addition
of saturated aqueous NaHCO$_3$ (50mL), and the aqueous layer was
extracted with EtOAc (3 (30 mL). The combined organic
extracts were washed with H$_2$O (4 (50 mL), dried (Na$_2$SO$_4$), and
concentrated under reduced pressure. Flash chromatography
(SiO$_2$, 3 (10 cm, 0-20% EtOAc/hexane gradient) yielded **11g**
(0.681 g, 96%) as a colorless mixture of rotamers: ^{1}H NMR
(CDCl$_3$, 400 MHz) 2:1 rotamers δ 6.15-6.03 (m, 1H), 6.00-5.90
(m, 1H), 5.11-5.03 (m, 2H), 4.17-3.87 (m, 2H), 3.77 and 3.74
(s, 3H), 3.65 and 3.63 (s, 3H), 3.627 and 3.622 (s, 3H), 2.14
and 2.13 (s, 3H), 1.50 and 1.34 (s, 9H); ^{13}C NMR (CDCl$_3$, 100
MHz) rotamers δ 153.65 and 153.62, 152.8 and 152.1, 151.0 and
150.7, 147.0 and 146.7, 134.5 and 134.0, 129.5 and 129.0,
127.0 and 126.7, 121.0 and 120.6, 99.0, 97.7 and 97.3, 80.8
and 80.6, 60.5 and 60.4, 60.3 and 60.2, 58.5 and 58.4, 50.4,
48.8, 28.3 and 28.2, 9.9; IR (film) ν$_{max}$ 2973, 2936, 1704,
1456, 1366 cm^{-1}; FABHRMS (NBA/CsI) m/z 659.9655 (C$_{19}$H$_{27}$ClINO$_6$ +
Cs$^+$ requires 659.9626).
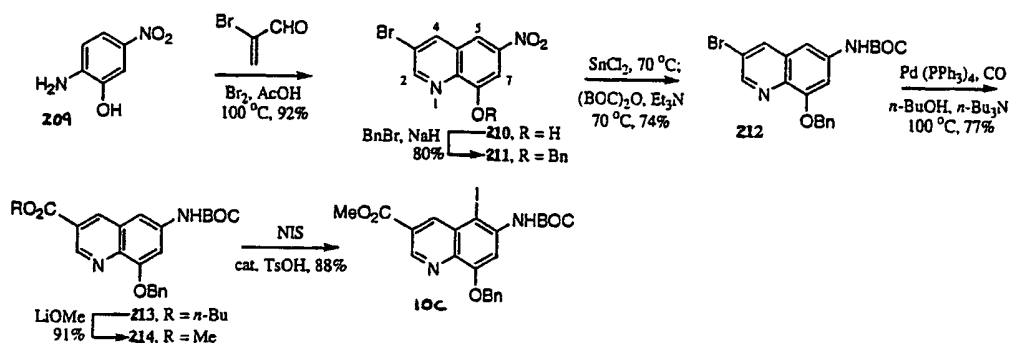
3-Bromo-8-hydroxy-6-nitroquinoline (210).

A solution of 2-bromoacrolein (5 g, 37.0 mmol, 1 equiv) in 110 mL glacial acetic acid at 25 °C was titrated to the appearance of a faint reddish color with bromine (ca. 5.9 g, 37.0 mmol, 1 equiv). 2-Hydroxy-4-nitroaniline (**209**, 5.7 g, 37.0 mmol, 1 equiv) was added, and the solution was gradually heated to 100 (C. The solution was cooled to 25 (C after one hour. Filtering and neutralization of the precipitate with 1 M sodium phosphate buffer (pH 7, Na_2HPO_4-NaH_2PO_4) afforded 9.2 g (9.95 g theoretical, 92%) of **210** as a light yellow solid: mp 240-241 (C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.93 (d, J = 2.0 Hz, 1H), 8.50 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 2.2 Hz, 1H), 8.18 (s, 1H), 7.92 (s, J = 2.3 Hz, 1H); ^{13}C NMR (DMSO, 62.5 MHz) δ 155.1, 152.1, 146.3, 139.5, 139.1, 128.7, 119.1, 113.5, 105.1; IR (film) ($_{max}$ 3408 (br), 3089, 1587, 1553, 1519, 1476, 1389, 1350, 1297, 1263, 1210, 1133, 1079, 929, 931, 839, 804, 734, 633 cm^{-1}; ESIMS m/z 269 (M + H$^+$, C_9H_3BrO requires 269); Anal. Calcd for C_9H_3BrO: C, 40.18; H, 1.87; N, 10.41. Found: C, 40.21; H, 1.91; N, 9.98.

8-(Benzyloxy)-3-bromo-6-nitroquinoline (211). A solution of **210**

(13.7 g, 51 mmol, 1 equiv) in anhydrous DMF (150 mL)

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was cooled to 4 (C under nitrogen and treated with KI (1.7 g,
10 mmol, 0.2 equiv) and sodium hydride (60% dispersion in oil,
2.24 g, 56 mmol, 1.1 equiv). Benzyl bromide (7.3 mL, 6.1
mmol, 1.2 equiv) was added after 30 min and the reaction was
allowed to warm to 25 (C. After 24 h, the reaction volume was
reduced by one-third *in vacuo* and EtOAc (200 mL) was added.
The reaction mixture was poured on H$_2$O (200 mL) and extracted
with EtOAc (3 (100 mL). The combined organic extracts were
washed with saturated aqueous NaCl (1 (40 ml), dried (Na$_2$SO$_4$)
and concentrated. Flash chromatography (SiO$_2$, 5.5 (20 cm, 50–
100% CH$_2$Cl$_2$-hexane) afforded **211** (15.63 g, 18.32 g theoretical,
85%) as a yellow solid: mp 170 (C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ
9.06 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 2.2 Hz, 1H), 8.25 (d,
J = 2.2 Hz, 1H), 7.83 (d, J = 2.2 Hz, 1H), 7.52 (app d, J =
7.4 Hz, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 5.47 (s, 2H); ^{13}C NMR
(CDCl$_3$, 62.5 MHz) δ 155.4, 153.3, 146.4, 140.3, 138.8, 135.0,
128.7 (2C), 128.6, 128.4 (2C), 127.5, 119.9, 115.1, 103.3,
71.4; IR (film) ($_{max}$ 3082, 3055, 2933, 2871, 1609, 1567, 1519,
1476, 1450, 1375, 1338, 1311, 1252, 1135, 1093, 976, 912, 842,
741 cm^{-1}; FABHRMS (NBA/NaI) m/z 359.0040 (M + H$^+$, C$_{16}$H$_{11}$BrN$_2$O$_3$
requires 359.0031). Anal. Calcd for C$_{16}$H$_{11}$BrN$_2$O$_3$: C, 53.50; H,
3.09; N, 7.80. Found: C, 53.81; H, 3.23; N, 7.48.

**8-(Benzyloxy)-3-bromo-6-*N*-(tert-butyloxycarbonyl)aminoquinolin
e (212).** A solution of **211** (200 mg, 0.56 mmol, 1 equiv) in
EtOAc (1.1 mL) at 25 (C was treated with SnCl$_2$-2H$_2$O (628 mg,
2.78 mmol, 5 equiv). The reaction mixture was heated to 70 (C
under nitrogen until an orange slurry formed (ca. 0.5 h).
After cooling to 25 (C, the reaction mixture was poured on ice
and made basic with 1N NaOH. The aqueous layer was filtered
and extracted with EtOAc (3 (15 mL). The combined organic
layers were treated with saturated aqueous NaCl (1 (10 mL),

dried (Na_2SO_4) and concentrated. The yellow solid was placed
under vacuum for 0.5h and then dissolved in anhydrous dioxane
(5 mL) and treated with di-tert-butyl dicarbonate (490 mg,
2.25 mmol, 4.0 equiv) and triethylamine (156 μL, 1.12 mmol,
2.0 equiv). The reaction mixture was warmed to 70°C under
argon for one day. After cooling, the solvent was removed *in
vacuo*. Chromatography (SiO_2, 3 (13 cm, 25% EtOAc-hexane)
afforded **212** (179 mg, 240 mg theoretical, 74%) as a light
yellow solid: mp 162 (C; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.77 (d, *J*
= 2.0 Hz, 1H), 8.13 (d, *J* = 2.5 Hz, 1H), 7.47 (app d, *J* = 7.5
Hz, 2H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.35 (m, 2H), 7.28 (m, 1H),
7.01 (d, *J* = 2.0 Hz, 1H), 6.61 (s, 1H), 5.37 (s, 2H), 1.51 (s,
9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.9, 152.4, 148.3, 137.9,
136.3, 136.2, 135.4, 131.0, 128.6 (2C), 128.0, 127.3 (2C),
118.6, 104.7, 103.6, 81.1, 70.9, 28.3 (3C); IR (film) ($_{max}$
3354, 2971, 2919, 1807, 1766, 1724, 1621, 1450, 1367, 1310,
1253, 1217, 1160, 1123, 1061, 843, 771, 699, 657 cm^{-1}; FABHRMS
(NBA/CsI) *m/z* 429.0825 (M + H^+, $C_{21}H_{21}BrN_2O_3$ requires 429.0814).

**n-Butyl8-(benzyloxy)-6-*N*-(tert-butyloxycarbonyl)aminoquinoline
-3-carboxylate (213).**

A solution of **212** (4.4 g, 10.1 mmol, 1 equiv) in 85 mL
n-BuOH was cooled to −78 (C and degassed under vacuum.
$Pd(PPh_3)_4$ (1.2g, 1.0 mmol, 0.1 equiv) and *n*-Bu_3N (2.9 mL, 12.1
mmol, 1.2 equiv) were added and the solution was purged with
nitrogen. The reaction mixture was then flushed with carbon
monoxide and then slowly heated to 100 (C under a CO
atmosphere. Upon complete reaction (ca. 12 h), 50 mL H_2O and 50
mL saturated aqueous NH_4Cl were added. The organic layer was
separated and the aqueous layer was extracted with EtOAc (3 (
50 mL). The combined organic layers were washed with
saturated aqueous NaCl (1 (40 mL), dried (Na_2SO_4) and

concentrated. Chromatography (SiO_2, 5.5 (20 cm, 25%
EtOAc-hexane) afforded **213** (3.55 g, 4.55 g theoretical, 78%)
as a yellow solid: mp 135-136 (C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ
9.31 (d, J = 2.0 Hz, 1H), 8.66 (d, J = 2.1 Hz, 1H), 7.61 (d,
J = 1.8 Hz, 1H), 7.49 (app d, J = 7.4 Hz, 2H), 7.35 (app t,
J = 7.2 Hz, 2H), 7.29 (m, 1H), 7.11 (d, J = 2.1 Hz, 1H), 6.64
(br s, 1H), 5.39 (s, 2H), 4.38 (t, J = 6.6 Hz, 2H), 1.78 (m,
2H), 1.52 (s, 9H), 1.49 (m, 2H, buried under 1.52 ppm), 0.98
(t, J = 7.4 Hz, 3H); ^{13}C NMR (acetone d_6, 100 MHz) δ 165.7,
155.7, 153.5, 146.8, 139.8, 139.5, 137.8, 137.7, 129.5, 129.1
(2C), 128.6, 128.4 (2C), 124.8, 107.1, 106.9, 80.4, 71.2,
65.5, 31.3, 28.3 (3C), 19.8, 13.9. IR (film) ($_{max}$ 3222, 3049,
2958, 2930, 2876, 1717, 1617, 1544, 1503, 1430, 1362, 1271,
1239, 1157, 1065 cm^{-1}; FABHRMS (NBA/CsI) m/z 451.2249 (M + H$^+$,
$C_{26}H_{30}N_2O_5$ requires 451.2233).

Methyl-8-(benzyloxy)-6-N-(tert-butyloxycarbonyl)aminoquinoline
-3-carboxylate (214). A solution of **213** (2.9g, 6.4 mmol, 1.0
equiv) in 70 mL MeOH was cooled to 4 (C under nitrogen and
treated with LiOMe (275 mg, 7.1 mmol, 1.1 equiv). The
reaction mixture was allowed to warm to 25 (C after 20 min.
Upon complete reaction (ca. 1.5 h), 100 mL H_2O was added. The
organic layer was separated and the aqueous layer was
extracted with EtOAc (3 (30 mL). The organic layers were
combined, washed with saturated aqueous NaCl (1 (30 mL),
dried (Na_2SO_4) and concentrated. Chromatography (SiO_2, 5 (19
cm, 25 - 30% EtOAc-hexane) afforded **214** (2.39 g, 2.63 g
theoretical, 91%) as a yellow solid: mp 173-174 (C; ^{1}H NMR
($CDCl_3$, 400 MHz) δ 9.29 (d, J = 2.0 Hz, 1H), 8.66 (d, J = 2.1
Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H,), 7.45 (m, 2H), 7.30 (m,
2H), 7.25 (m, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.85 (s, 1H),
5.36 (s, 2H), 3.98 (s, 3H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 125
MHz) δ 165.9, 154.6, 152.6, 146.9, 138.6, 137.9, 137.8, 136.0,

128.5, 128.4 (2C), 127.9, 127.3 (2C), 123.8, 106.5, 105.5,
80.8, 70.8, 52.4, 28.2 (3C); IR (film) ($_{max}$ 3333, 3241, 2974,
1723, 1621, 1580, 1539, 1497, 1431, 1390, 1364, 1277, 1231,
1164, 1126, 1103, 1062, 1000, 882, 846, 795, 749, 697, 662
cm^{-1}; FABHRMS (NBA/CsI) m/z 409.1773 (M + H$^+$, $C_{23}H_{24}N_2O_5$ requires
409.1763).

**Methyl 8-(benzyloxy)-6-[N-(tert-butyloxycarbonyl)amino]-5-
iodoquinoline-3-carboxylate (10c).**

A solution of **214** (2.13 g, 5.2 mmol, 1 equiv) in 85 mL of
a 1:1 mixture of THF-CH$_3$OH was cooled to 4 (C and treated with
40 mg TsOH (or H$_2$SO$_4$) in 0.5 mL THF. N-Iodosuccinimide (1.4 g,
6.2 mmol, 1.2 equiv) in 10 mL THF was then slowly added over
10 min. After 1.5 h, the reaction mixture was warmed to 25 (C
and then stirred 45 h. Upon complete reaction, 100 mL
saturated aqueous NaHCO$_3$, 100 mL Et$_2$O, and 100 mL H$_2$O were
added. The organic layer was separated and the aqueous layer
was extracted with Et$_2$O (3 (50 mL) and EtOAc (1 (50 mL). The
organic layers were combined, washed with saturated aqueous
NaHCO$_3$ (1 (50 mL) and saturated aqueous NaCl (1 (50 mL),
dried (Na$_2$SO$_4$) and concentrated. Chromatography (SiO$_2$, 5 (19
cm, hexanes then 30% EtOAc-hexane) provided **10c** (2.34 g, 2.78
g theoretical, 84%, typically 80-88%) as a yellow solid: mp
182-183 (C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 9.27 (d, J = 1.9 Hz,
1H), 8.96 (d, J = 1.9 Hz, 1H), 8.40 (s, 1H), 7.58 (m, 2H),
7.36 (m, 2H), 7.27 (m, 1H), 7.26 (s, 1H), 5.43 (s, 2H), 4.01
(s, 3H), 1.55 (s, 9H); ^{13}C NMR (CDCl$_3$, 62.5 MHz) δ 165.4,
155.0, 152.3, 147.6, 141.9, 139.8, 139.7, 135.8, 129.6, 128.5
(2C), 128.1, 128.0 (2C), 125.1, 105.6, 81.7, 78.4, 71.1,
52.6, 28.2 (3C); IR (film) ($_{max}$ 3384, 2974, 1723, 1595, 1554,
1498, 1431, 1400, 1359, 1328, 1262, 1226, 1149, 995, 754 cm^{-1};
FABHRMS (NBA/CsI) m/z 535.0743 (M + H$^+$, $C_{23}H_{23}IN_2O_5$ requires

535.0730).
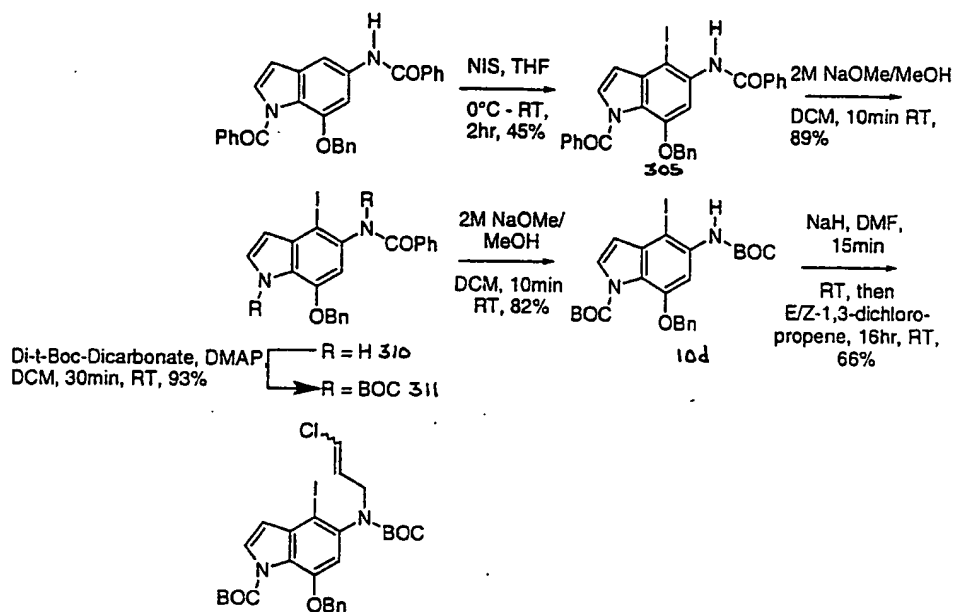
N^5,1-Dibenzoyl-5-amino-7-(benzyloxy)-4-iodoindole (305).

The above indole (118mg, 0.26mmol) was stirred in THF
(1mL) and toluenesulfonic acid (26mg, 0.13mmol) was added. The
solution was cooled to 0°C and N-iodosuccinimide (71mg,
0.312mmol) in THF (1mL) was added. The reaction was allowed to
warm to 25°C over 1 hr. After 16hr, a further portion of
N-iodosuccinimide (15mg, 0.065mmol) was added and the reaction
was stirred for a further 24hr. Saturated sodium bicarbonate
solution (1mL) and water (4mL) were then added and the
resulting mixture was extracted with chloroform (3 x 5mL). The
organic layers were combined, dried (MgSO$_4$) and volatiles were
removed under reduced pressure. The residue was purified by
flash column chromatography (silica, ethyl acetate/hexane 3:7,
2.5 x 15cm) and crystallized from ethyl acetate to give the
expected product (305) as a yellow solid (67mg, 45%); ^{1}H NMR

δ(ppm) (CDCl₃) 8.15 (s, 1H, NH), 7.99 (d, 2H J = Hz), 7.64 (d,
2H, J = Hz), 7.58-7.47 (m, 4H, ArH), 7.30-7.17 (m, 5H, ArH),
6.58 (d, 1H, J = 3.6Hz), 4.92 (s, 2H). 13C NMR δ(ppm) 168,
165.5, 147.3, 136.2, 135.8, 134.9, 134.7, 134.1, 132.2,
132.1,129.8, 129.6, 129.5, 129.0, 128.4, 128.3, 128.2, 127.8,
127.7, 127.1, 127.0, 122.4, 110.6, 102.1, 71.9, 70.6 IR (neat)
ν_{max} 3058, 1703, 1678, 1598, 1332, 1279, 1237, 695 cm⁻¹ Mass
Spectrum (FAB, NAB/CsI) 705 (M⁺+Cs⁺) .

N⁵-Benzoyl-5-amino-7-(benzyloxy)-4-iodoindole (310).

The above iodo-compound (305) (193mg, 0.34mmol) was
stirred in dichloromethane (10mL). Sodium methoxide in
methanol (0.523mL, 1.04mmol) was added and the solution was
stirred at RT for 10 min. Water (50mL) and ethyl acetate
(50mL) were added and organic layer was separated, dried
(MgSO₄) and evaporated to give the crude product.
Chromatography (2 x 15cm SiO₂, ethyl acetate/hexanes 1:3) gave
the pure compound (142mg, 89%), Rf 0.2 (SiO₂,, ethyl
acetate/hexanes 1:3) as a colourless solid: ¹H NMR (CDCl₃,
400MHz) 8.61 (s, 1H, NH), 8.31(s, 1H, NH), 8.05 (s, 1H), 8.00
(d, 1H, J = 6.8Hz), 7.53 (m, 5H), 7.37 (m, 3H), 7.21 (dd, 1H,
J = 2.8, 1.4Hz), 6.43 (dd, 1H, J = 2.7, 1.2Hz), 5.28 (s, 2H);
IR (neat) ν_{max} 3290, 3010, 1658, 1573, 1535, 1355 cm⁻¹; FABHRMS
(NBA-CsI) m/z   600.9408.(M +Cs⁺, C₂₂H₁₇IN₂O₂ requires 600.9389).

N⁵-Benzoyl-N⁵,1-di-(tert-butoxycarbonyl)-5-amino-7-(benzyloxy)-4-iodoindole (311).

Di-tert-butyl dicarbonate (687mg, 3.16mmol) and DMAP
(128mg, 1.04mmol) were added to a stirred solution of compound
310 (255mg, 0.54mmol) in dichloromethane (6mL). After 30min at
RT the solution was directly subjected to chromatography (2 x
15cm SiO₂, ethyl acetate/hexane 1:4) to give the pure product

(390mg, 93%) as a colorless oil (Rf 0.80, SiO_2, ethyl
acetate/hexane 1:3); ^{1}H NMR ($CDCl_3$, 400MHz) 7.81 (d, 2H, J =
6.9Hz), 7.55 (d, 1H, J = 3.6Hz), 7.45 (m, 5H), 7.31 (m, 3H),
6.82 (s, 1H), 6.57 (d, 1H, J = 3.6Hz), 5.15 (s, 2H), 1.47 (s,
9H), 1.22 (s, 9H); FABHRMS (NBA-CsI) m/z 801.0402 (M +Cs$^+$,
$C_{32}H_{33}IN_2O_6$ requires 801.0438).

N^5,1-Di-(*tert*-butoxycarbonyl)-5-amino-7-(benzyloxy)-4-iodoindol
e (10d).

Sodium methoxide in methanol (2M, 0.224mL, 0.44mmol) was
added to a stirred solution of compound (**311**) (150mg,
0.22mmol) in dichloromethane (5mL). After 10 min at RT, water
(25mL) and ethyl acetate (25mL) were added and the organic
layer was separated. The aqueous layer was extracted with
ethyl acetate (25mL) and the combined organic layers were
dried ($MgSO_4$) and concentrated. Chromatography (2 x 15cm
SiO_2,gradient elution ethyl acetate/hexanes 1:9 to ethyl
acetate/hexanes 1:3) gave the pure compound (102mg , 82%), Rf
0.8 (SiO_2,, ethyl acetate/hexanes 1:3) as a colourless oil: ^{1}H
NMR ($CDCl_3$, 400MHz) 7.83 (br s, 1H, NH), 8.00 (d, 1H, J =
6.8Hz), 7.53 (m, 3H (1H + 2H), 7.37 (m, 3H), 6.84 (br s, 1H),
6.45 (d, 1H, J = 3.4Hz), 5.21 (s, 2H), 1.54 (s, 9H), 1.45 (s,
9H);IR (neat) ν_{max} 3395, 2977, 1759, 1727, 1603, 1577, 1517,
1367, 1346, 1228, 1154, 1111 cm^{-1}; FABHRMS (NBA-CsI) m/z
697.0176 (M +Cs$^+$, $C_{25}H_{29}IN_2O_5$ requires 697.0176).

N^5-(3-Chloro-2-propen-1-yl)-N^5,1-di-((*tert*-butyloxy)carbonyl)-5
-amino-7-(benzyloxy)-4-iodoindole (11d).

Sodium hydride (22mg, 0.54mmol, 3eq, 60% dispersion) was
added to a stirred solution of compound (10d) (100mg,
0.18mmol) in DMF (5mL). After 15 min at RT,
E/Z-1,3-dichloropropene (0.025mL, 0.27mmol) was added. The

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solution was stirred at Rt for 1hr. Water (50mL) and ethyl
acetate (50mL) were then added and the organic layer was
separated. The aqueous layer was extracted with ethyl acetate
(50mL) and the combined organic layers were dried (MgSO$_4$) and
concentrated. Chromatography (2 x 15cm SiO$_2$, ethyl
acetate/hexanes 1:9) gave the pure compound (75.4mg , 66%) as
a mixture of E and Z isomers: ^{1}H NMR (CDCl$_3$, 400MHz) major
rotamer 7.47 (br s, 1H), 7.36 (m, 5H), 6.53 (m, 1H), 6.00 (m,
2H), 5.17 (s, 2H), 4.51 (m, 1H), 4.11 (m, 1H), 1.54 (s, 9H),
1.25 (s, 9H); IR (neat) ν_{max} 2976, 1759, 1701, 1630, 1570,
1367, 1157 cm^{-1}; FABHRMS (NBA-CsI) m/z 771.0125 (M +Cs$^+$,
C$_{28}$H$_{32}$ClIN$_2$O$_5$ requires 771.0099)

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What is claimed:

1.   A method for the synthesis of a dihydroindole C-ring of a
CC-1065 / duocarmycin analog wherein the method comprises the
5   steps of:

        Step A: alkylating an aryl halide with 1,3-
        dichloropropene and a catalytic amount of n-
        tetrabutylammonium iodide for forming a vinyl chloride;
        then

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        Step B: cyclizing the vinyl chloride of said step A under
        conditions using tribuytyl tin hydride, catalytic AIBN
        and toluene as the solvent for forming the dihydroindole
        C-ring of the CC-1065 / duocarmycin analog.

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    2.   A compound represented by the following structure:

20

    3.   A compound represented by the following structure:

25
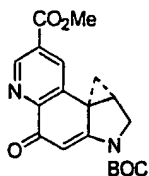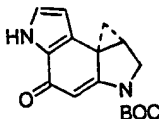
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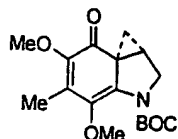
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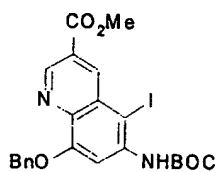
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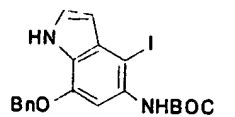
7.   A compound represented by the following structure:

8.   A compound represented by the following structure:

OMOM

MeO

I

Me

NHBOC

OMe

5

9.   A compound represented by the following structure:

Cl

I

BnO

N
BOC
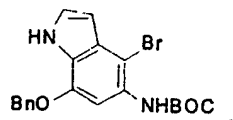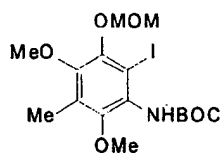
10. A compound represented by the following structure:

10

CN

Cl

I

BnO

N
BOC
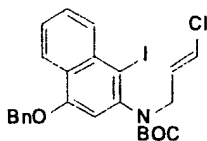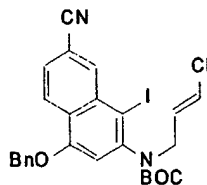
11. A compound represented by the following structure:

CO_2Me

Cl

N

I

BnO

N
BOC
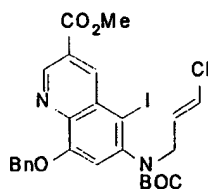
12. A compound represented by the following structure:
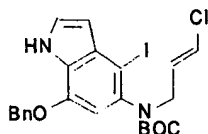
5 13. A compound represented by the following structure:
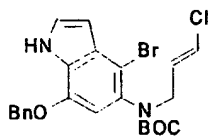
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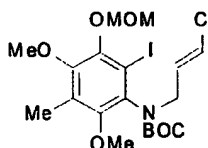
10

15. A compound represented by the following structure:
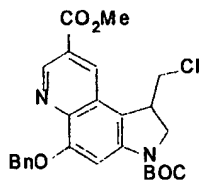
16. A compound represented by the following structure:

15
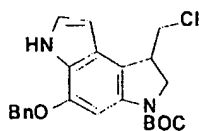
17. A compound represented by the following structure:
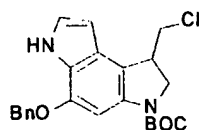
5 18. A compound represented by the following structure:
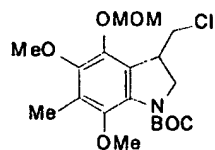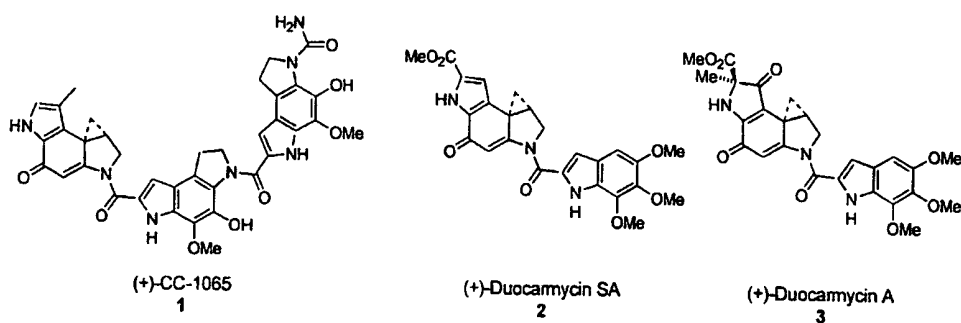
FIGURE 1
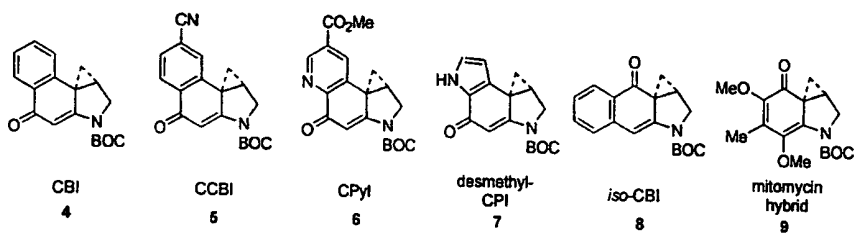
FIGURE 2
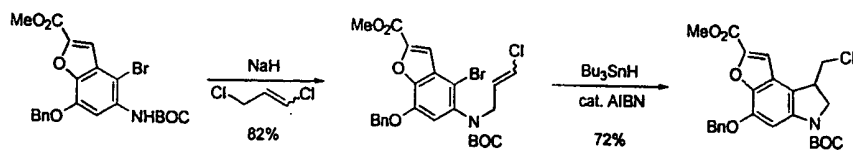
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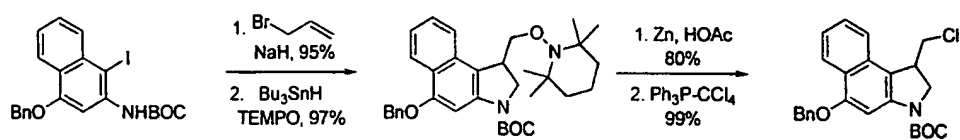
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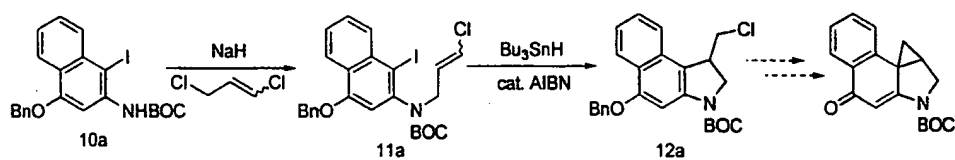
FIGURE 5
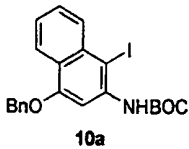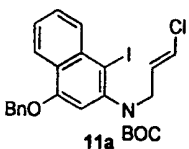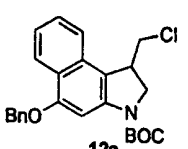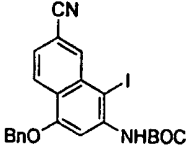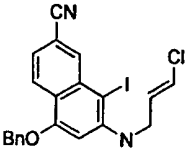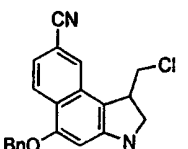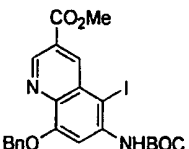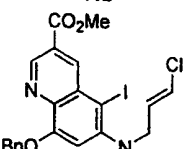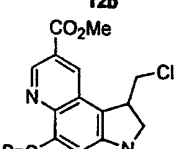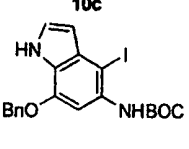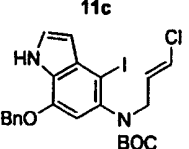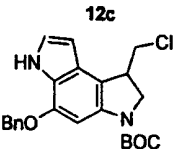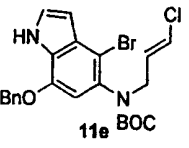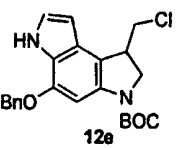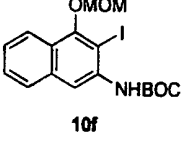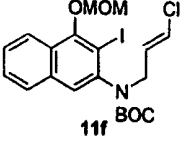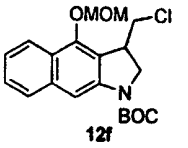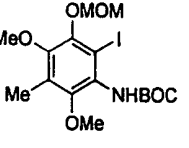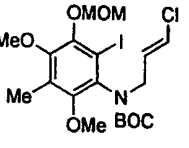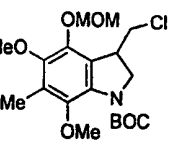
Entry	Aniline (10)	Conditions	Product (11)	Yield	Conditions	Indoline (12)	Yield
1	10a	a	11a	98%	c	12a	90%
2	10b	a	11b	88%	c	12b	85%
3	10c	a	11c	94%	c	12c	82%
4	10d	a	11d	70%	d	12d	72%
5	10e	a	11e	49%	d	12e	77%
6	10f	b	11f	96%	c	12f	96%
7	10g	b	11g	96%	c	12g	96%

FIGURE 6